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Demonstration of a stabilized pyramidal nitrogen (sp^3) in an acyclic system by ^{1}HNMR spectroscopy: A strong repulsive interaction between the lone electron pair and a phenyl ring

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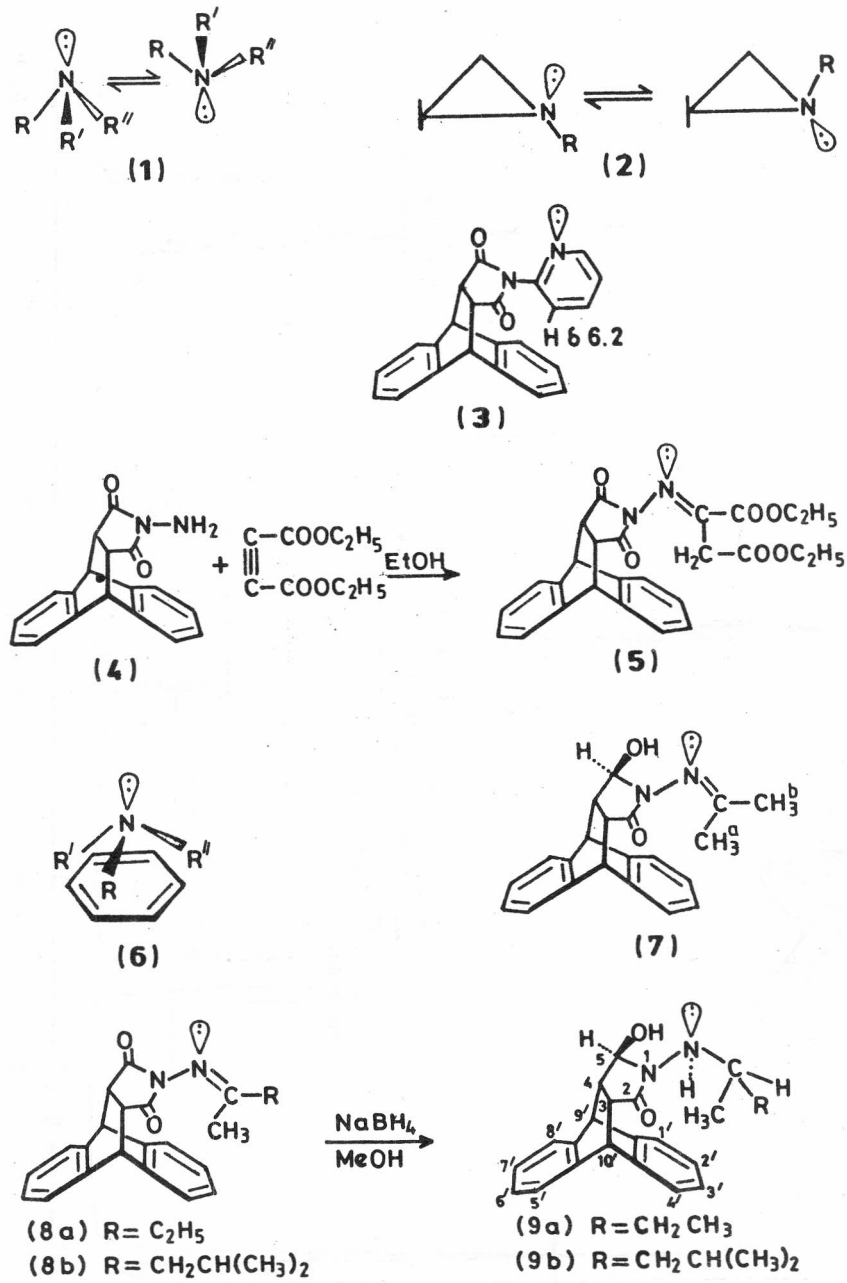
Condensation of butanone-2 and 4-methylpentanone-2 with N-amino-2,3-(9′,10′-dihydroanthracene-9′,10′-diyl)succinimide gives only one isomeric form of hydrazones which are assigned *E*-configuration. With an excess of sodium borohydride in methanol, one of the carbonyls of the hydrazone is reduced to $-CHOH$ and the $-N=CCH_3R$ is transformed into $-NH-CHCH_3R$. Highly shielded N′-alkyl protons in ^{1}H NMR indicate that N′-alkyls are right over the cage phenyl ring, which would result from the non-inverting pyramidal geometry of the exocyclic nitrogen. A strong repulsion between the lone electron pair of Nsp^3- and the π-electrons of the phenyl ring has been attributed to the restricted inversion of pyramidal nitrogen. Diastereomeric nature of the methyl protons indicates two conformations about Nsp^3-Csp^3 bond which have been shown in the population ratio of 1:2. The -OH group of the pyrrolidine ring has been proposed to be *exo*-to the cage. 5-Acetoxy-N′-acetyl, derivative exhibits restricted rotation about the N-N bond and a preferred conformation with the N′-alkyl in *syn*-orientation, which supports the proposed stereochemistry of the $-OH$ group.

In general the rate of pyramidal inversion of nitrogen **1** in amines of the type R_3N is too fast (of the order 10^{11}/sec) to be measured by ^{1}H NMR spectroscopy[1,2]. Nitrogen atoms invert slowly in a three membered ring **2**[2,3] and also when connected with another atom bearing an unshared pair of electrons[4,5]. Conformational analysis about the N-C (pyridyl) bond in **3** has shown that 'effective size' of the sp^2 lone electron pair of nitrogen[6] is sufficient to restrict rotation about the N-C bond and the pyridyl nitrogen remains in the *anti*-orientation to the cage[7]. The addition compound obtained from N-amino-2,3-(9′,10′-dihydroanthracene-9′,10′-diyl)succinimide **4** and diethyl acetylenedicarboxylate has been shown to be an azomethine[8] **5**. These observations indicated a strong electrostatic repulsion of the sp^2 lone electron pair from the phenyl ring. On these considerations it was proposed to hold an sp^3-nitrogen over a phenyl ring **6** which may restrict pyramidal inversion. Recently a pyramidal geometry of nitrogen in **7** was demonstrated in solution having its lone electron pair in *anti*-orientation with the help of ^{1}H NMR spectroscopy[9]. X-Ray crystallographic studies have established the sp^3-geometry of the exocyclic nitrogen in **7** in the solid state. In this paper we report the geometry of compounds **9** obtained by the reduction of **8** with sodium borohydride in methanol on the basis of ^{1}H NMR spectral studies. N′-Methine carbon contains dissimilar and bulky substituents and the high resolution (500 MHz) spectrum has been helpful in resolving the complicated pattern.

Condensation of N-aminosuccinimidyl compound **4**[10] and 2-butanone in ethanol yielded **8a**. The ^{1}H NMR of **8a** exhibits a sharp singlet at δ 0.80 (3H) for the methyl protons and a normal triplet (δ 1.05, 3H) and a quartet (δ 2.32, 2H) for the ethyl protons along with other resonances. The spectral pattern indicated restricted rotation about the N-N bond and the imine part, $-N=C(C_2H_5)(CH_3)$ orthogonal to the succinimidyl plane[11]. Methyl resonances at a shielded position suggested it to be in *syn*-orientation and the presence of an exclusive *E*-configuration of the product. Compound **8a** remains unchanged when boiled in xylene which further indicated the stability of *E*-configuration[12]. Reduction of **8a** with an excess of sodium borohydride in methanol yielded **9a** in which one of the succinimidyl carbonyls is reduced to $-CHOH$ and the imine part is transformed into $-NH\text{-}CH(CH_3)(C_2H_5)$.

The ^{1}H NMR spectrum of **9a** exhibits highly characteristic absorption for the 2-butylamino protons in the region δ 0.35-0.85 (Figure 1). The doublets at δ 0.35 and 0.67 in the intensity ratio



of 1:2 have been assigned to the CH_3-CH-group. Resonances at δ 0.58 (narrow multiplet), 0.70 (triplet) and 0.85 (broad multiplet) have been attributed to the ethyl group, ($-CH_2$-CH_3). Considering the shielding parameters of the N-isobutyl protons, it is evident that the N-alkyls are sitting right over the cage phenyl ring which would be possible with the non-inverting geometry of the exocyclic nitrogen. The spectral pattern clearly demonstrates the phenomenon of restricted pyramidel inversion of nitrogen resulting from a strong electronic repulsive interaction of the lone electron pair with the cage phenyl ring.[9]

The duplexity in the $-CH_3$ and the CH_2-CH_3 resonances suggests the presence of two conformations about the $N_{sp}{}^3$-$C_{sp}{}^3$ bond. With the pyramidal geometry of nitrogen, two conformations **10a** and **11a** about the N-C bond would be possible. In the conformation **10a**, the $-CH_3$ doublet appears at δ 0.35 while the triplet of $-CH_2$-CH_3 resonates at δ 0.70. In the conformation **11a**, CH_3-has been assigned the signal at δ 0.67 and the CH_3-CH_2 at 0.58. The triplet of the methyl is overlapped by the methylene protons multiplet. In the two conformations $-CH_2$- appears as multiplets at δ 0.58 and 0.85. 500 MHz spectrum has

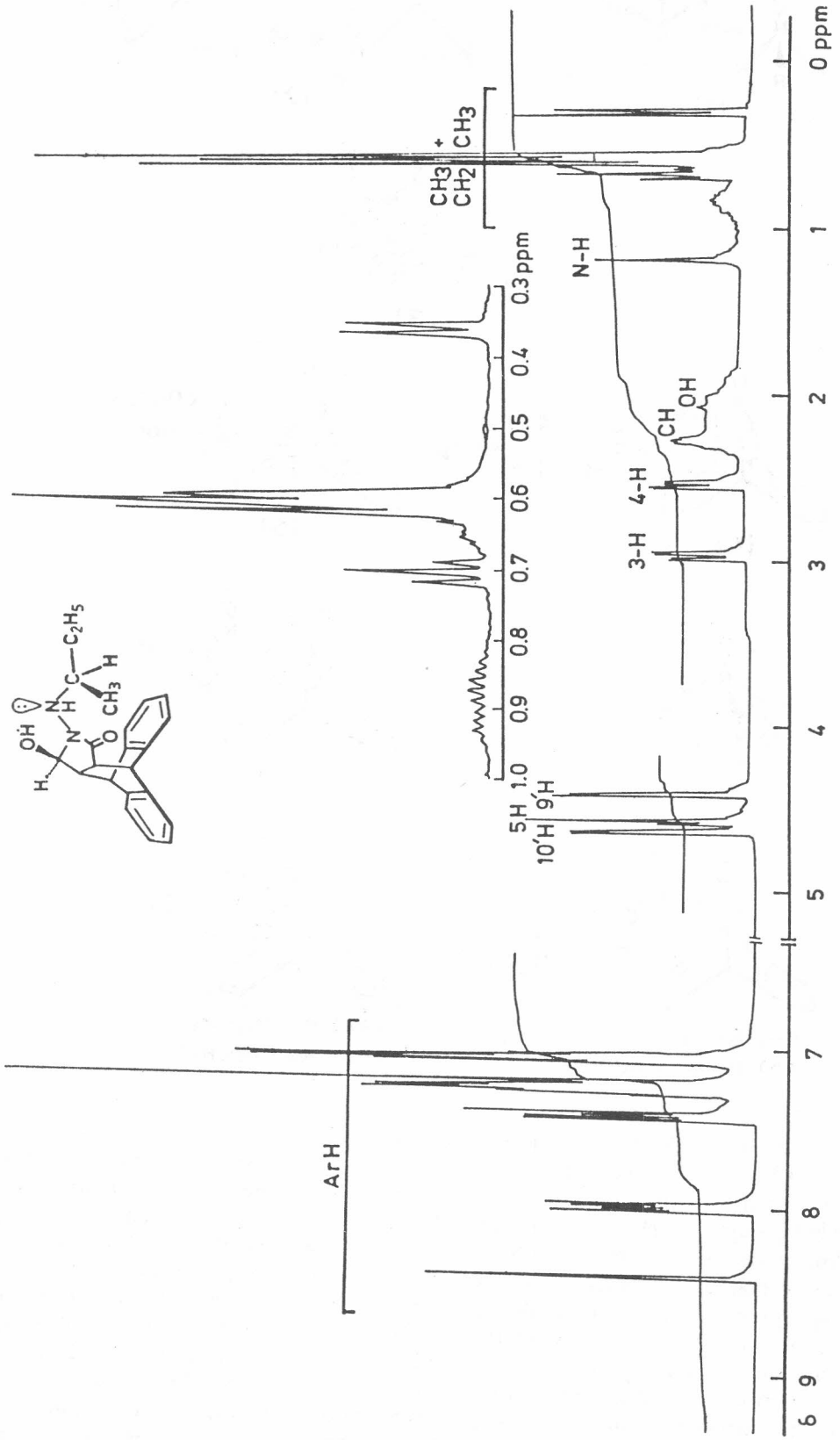
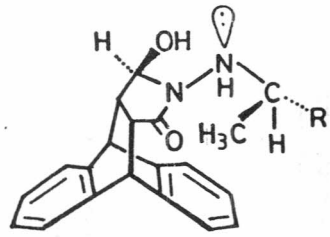
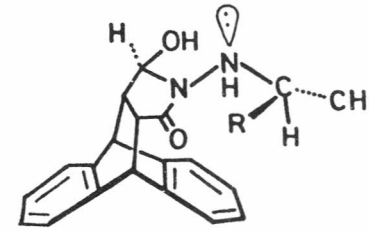


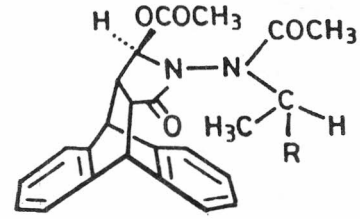
Figure 1—270 MHz ^{1}H NMR spectrum of compound **9a** in $CDCl_3$. The inset spectrum has been recorded at 500 MHz.



(10a) R = C_2H_5
(10b) R = $CH_2CH(CH_3)_2$



(11a) R = C_2H_5
(11b) R = $CH_2CH(CH_3)_2$



(12a) R = CH_2CH_3

been helpful in resolving N-CH, CH_3-CH and CH_3-CH_2- resonances (Figure 1). The COSY spectrum (2-D NMR, 500 MHz) of compound **9a** exhibits more than two couplings for the methine protons, $-NH-CH(CH_3)$ CH_2-CH_3 (δ 2.3) and supports the diastereomeric nature of the methyl group (Figure 2).

During the reduction of **8a** with sodium borohydride one of the carbonyls is reduced to $-CHOH$ group. Only one isomeric product was obtained and the *exo*-configuration (in the *exo* configuration, the - OH group is away from the cage) of the - OH group has been proposed. Acetylation of **9a** gave 5-acetoxy - N′ - acetyl derivative **12a** where the exocyclic nitrogen is transformed into sp^2 state and exhibited the usual restricted rotation and nonplanar conformation about the N-N bond in its ^{1}HNMR spectrum[14]. A preferred conformation with the N′-isobutyl group in *syn*-orientation (towards the cage) having the magnetic environment similar to that in **9a** and N′-acetyl in *anti*-orientation (away from the cage) is exhibited. Normal *O*-acetyl resonances indicate that it is not influenced by the anisotropy of the cage and support the *exo*-configuration of the - OH group. The X-ray crystallographic studies of **7** has demonstrated that $-OH$ group remains in the *exo*-orientation. The *exo*-orientation of the $-OH$ group suggests the hydride attack on the carbonyl from the *endo* side which seems to be very hard due to steric repulsion of the phenyl group. It appears that the reduction occurred from the *exo*-side and then the *endo*-hydroxy compound was isomerized to *exo*-hydroxy compound by thermodynamic control through the ring opened intermediate.

Condensation of 4-methylpentanone-2 with N-amino compound **4** in ethanol gave the product **8b**. It exhibited a sharp singlet at δ 0.77 (3H) and normal resonances for the isobutyl protons. It indicated the presence of *E* isomeric form of the hydrazone. Reduction of **8b** with the excess of sodium borohydride in methanol yielded **9b**. In this process one of the carbonyls of the succinimidyl ring is reduced to $-CHOH$ and the $-C=N$ is transformed into $-CH-NH-$. The spectral pattern of **9b** is quite characteristic and similar to **8b**. N′-Alkyl protons resonate at δ 0.30-1.14 (12H,m) and suggested the sp^3-geometry of exocyclic nitrogen. A doublet at δ 0.30 (1H) further suggests the presence of two conformations **10b** and **11b** about the $N_{sp}{}^3$ - $C_{sp}{}^3$ bond in the population ratio of 1:2.

Experimental Section

General. All melting points reported are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q multinuclear spectrometer at 25°C in $CDCl_3$. ^{1}H NMR (270 MHz and 500 MHz) of **9a** and **12a** were obtained from the University of Minnesota, USA. IR spectra were recorded as Nujol mulls on a Perkin-Elmer 720 spectrometer. ^{1}H NMR spectral data are given in Table I.

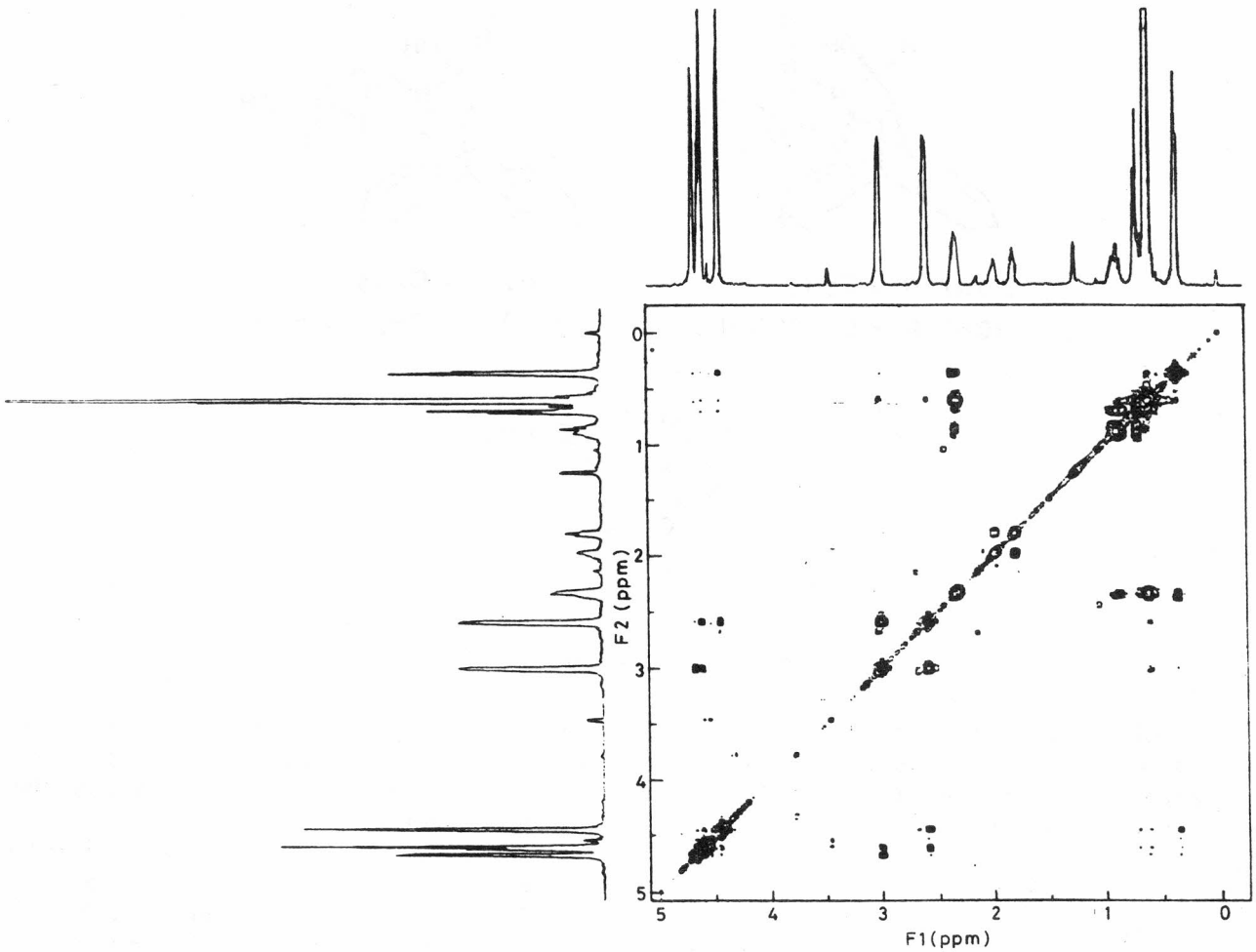


Figure 2—COSY spectrum (2-D NMR) of compound **9a** at 500 MHz.

Compound 8a [N-(2-butylideneamino)-3, 4-endo-(9′, 10′-dihydroanthracene-9′, 10′-diyl)succinimide]. It was prepared by refluxing the N-amino-imide of the anthracene maleic anhydride adduct **4**[10] with an equimolar amount of butanone-2 in ethanol for 4 hr. On cooling, the product separated out which was recrystallized from ethanol. The product showed a single spot on TLC plate. M.p. 154-56°, yield, 60%. Anal. Calcd. for $C_{22}H_{20}O_2N_2$: C, 76.74 and H, 5.81. Found: C, 76.82 and H, 5.72%. IR: 1780 (m), 1700 (s), 1630(m) cm^{-1}.

Compound 8b. It was obtained by refluxing the N-amino compound **4** with an equimolar amount of 4-methylpentanone-2 in ethanol in the same way as mentioned for **8a**. It showed a single spot on TLC plate and melted at 200-202°, yield 55%. Anal. Calcd for $C_{24}H_{24}O_2N_2$: C, 77.41, H, 6.58. Found: C, 77.36, H, 6.38%. IR: 1775 (w), 1700(s), 1640(m) cm^{-1}.

Compound 9a [N-(1-methylpropylamino)-3,4-*endo*-(9′10′-dihydroanthrance-9′,10′diyl)-5-*exo*-hydroxy-2-pyrrolidone]. The hydrazone **8a** was dissolved in excess of methanol and sodium borohydride (4 mmoles) added to it in parts while stirring the mixture over a period of 30 min. The contents were kept for 6 hr, at room temperature. The borate complex was hydrolysed with water and the product extracted with diethyl ether. The extract was dried over anhydrous sodium sulphate and on concentration a crystalline product was obtained, m.p. 185-86°, yield 35%. Anal. Calcd for $C_{22}H_{24}O_2N_2$: C, 75.86, H 6.58%. Found C, 75.72%, H, 6.48; IR: 3430(m), 3160(m), 1670(s).

Compound 9b. It was obtained by the reduction of **8b** with sodium borohydride in methanol in a similar way as reported for **9a**. M.p. 255-57°, yield 30%. Anal. Calcd for $C_{24}H_{28}O_2N_2$: C, 76.59,

Table I—^{1}H NMR spectral data of some compounds

Compd	(^{1}H NMR (δ, ppm) (90 MHz))
8a	CH_3-C), 1.05 (3H, t, CH_2CH_3, J=6.5 Hz), 2.32 (2H, q, CH_2-CH_3, J=6.5 Hz), 3.25 (2H, bs, 3- and 4-H), 4.81 (2H, bs, 9′-,10′-H), 7.25-8.70 (8H, m, ArH).
8b	(90 MHz): 60.77 (3H, s, CH_3-), 0.93 [6H, d, $-CH-(CH_3)_2$], 2.0 [1H, m, $-CH(CH_3)_2$], 2.26 (2H, d, CH_2-CH), 3.40 (2H, bs, 3-, 4-H), 5.03 (2H, bs, 9′-, 10′-H), 7.35-8.75 (8H, m, ArH).
9a	(270 MHz): 60.35 (1H, d) and 0.60 (2H,d)($-CHCH_3$), 60.58 (3H, bm), 0.70 (1H, t) and 0.85 (1H, bm), 1.20 (1H, bs, N-H), 2.05 (1H, bs, O-H), 2.31 (1H, bm, −CH), 2.50 (1H, dd, 4-H), 3.0 (1H, dd, 3H), 4.33 (1H, d, 9′-H), 4.55 (1H, d, CH-OH), 4.6 (1H, d, 10′-H), 7.03-8.63 (8H, bm, ArH).
9b	(90 MHz): 60.30 (1H, d, CH_3-CH-), 0.6-1.1 (11H, complex m, CH_3-CH-CH_2-$CH(CH_3)_2$], 1.34 (1H, bs, N-H), 2.40 (1H, m, −CH-CH_2), 2.57 (1H, dd, 4-H), 3.20 (1H, dd, 3-H), 3.8 (1H, bs, −OH), 4.62 (1H, d,9′-H), 4.72 (1H, d, 5-H), 4.84 (1H, d, 10′-H, 7.28-8.66 (8H, m, ArH).
12a	(270 MHz): 60.45 (1H,d) and 0.70 (2H,d) (CH_3CH), 0.5-0.8 (5H, m, $-CH_2CH_3$), 2.1 (3H,s, N-$COCH_3$), 2.22 (3H, s, $-OCOCH_3$), 2.71 (1H, dd, 4-H), 3.21 (1H, dd, 3-H), 3.7(1H, m, $CHCH_3$), 4.7- (1H, d, 9′-H), 4.75 (1H, d, 10′-H), 5.81 (1H, s, CH-OAc), 7.1-8.7 (8H, bm, ArH).

H, 7.48%. Found: C, 76.35, H, 7.26; IR: 3420(m), 3160(m), 1670(s).

Compound 12a (1-[N-acetyl-N-(1-methylpropyl)]amino-3, 4-*endo*-(9′, 10′-dihydroanthracene-9′, 10′-dihydroanthracene-9′, 10′-diyl)-5-*exo*-acetoxy-2-pyrrolidone. It was obtained by refluxing **9a** with an excess of acetic anhydride for 2 hr. Excess of Ac_2O was removed *in vacuo* to give a solid which was recrystallized from ethanol, m.p. 175-76°. Anal. Calcd for $C_{26}H_{28}O_4N_2$:C, 72.20, H, 6.52%. Found C, 72.07, H, 6.40; IR: 1740(s), 1675(s) cm^{-1}.

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